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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/883,093	06/14/2001	Catherine Guenther	R-126	7936

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EXAMINER	
WILSON, MICHAEL C	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/883,093	GUENTHER ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sh t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *1-4,10,16,30,36 and 37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-9,11-15,17-29,31-35 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1-3*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group II, claims 1-15, 17-29 and 33 is acknowledged. However, the claims are wrong. Group II is claims 5-7, 9, 13-15 and 31-35. Upon reconsideration, Group III (claims 8, 11, 12, 17-29, 32-34 and 38) has been recombined with Group II.

Claims 1-4, 10, 16, 30 and 37 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Claim 36 remains withdrawn because it is so unclear.

Claims 5-9, 11-15, 17-29, 31-35 and 38 are under consideration.

Claim Objections

Claim 10 is objected to because it is dependent upon claim 1 which is not under consideration.

Specification

The amendment to the description of Fig. 2A-2B has been entered. However, the description remains unclear. The description should include the fact that Fig. 2A-2B shows the nuclear hormone receptor of SEQ ID NO:1. Correction is required.

The application numbers throughout the specification will require updating as necessary.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 5-9, 11-15, 17-29, 31-35 and 38 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility.

Claims 8, 17-29 and 38 are directed toward a transgenic animal having a disruption of a nuclear hormone receptor gene. Claims 11, 12 and 32-34 are directed toward using such a transgenic animal to test agents. The specification teaches making mice having a homozygous disruption in the nuclear hormone receptor of SEQ ID NO:1 (pg 51). The specification suggests using the mice as a model of disease, specifically as a model for infertility, glucose metabolism, diabetes, behavioral, neurological, neuropsychological, psychotic phenotypes (pg 18-20; pg 20, line 2). However, the specification does not disclose that neurological, neuropsychological or psychotic disease found in humans is linked to a disruption in the nuclear hormone receptor of SEQ ID NO:1. The mice had abnormalities in the spleen, thymus and lymph nodes (pg 52-53); however, the specification does not teach how to use such mice as a model of disease. The mice showed decreased performance in the rotarod test. However, the specification does not teach how to use such mice as a model of any disease or that a disruption in SEQ ID NO:1 in humans relates to a disease that causes decreased coordination. None of the phenotypes found by the tests correlate to a useful phenotype because the phenotypes described are not specific to a

disease and are not linked to a disruption in the human equivalent of SEQ ID NO:1. The results of the behavioral tests are also not statistically significant because the number of mice tested is not disclosed. The mice claimed cannot be used to determine compounds that modulate nuclear hormone receptor expression because nuclear hormone receptor is not expressed in the cells of the mice. Using the mice to determining whether a particular phenotype is ameliorated is not a specific or substantial utility because the specification does not link the phenotype to any specific disease or to a disease caused by a disruption in humans. The specification does not identify any compounds that ameliorate any condition using the mice. Thus, the specification does not provide a specific or substantial use for a mouse as claimed, specifically having the phenotypes recited in claims 17-29.

Claims 5-7, 9 and 31 directed toward cells having a disruption of a nuclear hormone receptor gene or a cell derived from the transgenic animal, and claims 13-15 and 35, directed toward using such cells to identify compounds, are included because the cells lack a specific and substantial utility for the reasons above, because the specification does not teach how to use the cells other than when they are part of a mouse that is a model of disease and because the specification does not teach how to make the cells in the absence of the mouse.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-9, 11-15, 17-29, 31-35 and 38 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use mice having abnormal pain threshold.

The specification does not teach how to make animals or cells having a disruption in a nuclear hormone receptor gene other than mice. Specifically, claims 6 and 7 encompass mice and rat cells. "Murine" encompasses mice and rats (http://www.m-w.com/cgi-bin/dictionary?book=Dictionary&va=murine). The only means of making a cell with a disruption in a nuclear hormone receptor gene taught in the specification is by using mouse embryonic stem cell technology. The state of the art at the time of filing was such that embryonic stem (ES) cell technology had only been successful in mice. Wagner (May 1995, Clin. and Experimental Hypertension, Vol. 17, pages 593-605) and Mullins (1996, J. Clin. Invest., Vol. 98, pages S37-S40) taught germline transmission of ES cells has not been demonstrated in species other than mice and the growth of ES cells from species other than mice is unreliable. Wall (1996, Theriogenology, Vol. 45, pg 57-68) taught transgene expression and the physiological result of such expression in livestock was not always accurately predicted in transgenic mice

(page 62, line 7). Since the time of filing, Zan (Nature Biotech, 2003, Vol. 21, pg 645-651) taught making knockout rats using mutagenized male rats, which was not taught in the specification and considered essential to making knockout rats. The specification fails to provide sufficient guidance to make transgenics other than mice by teaching obtaining ES cells in species other than mice. The specification does not teach the nucleic acid sequence of a nuclear hormone receptor gene in non-mice, non-human species or correlate the nuclear hormone receptor gene in mice to the nuclear hormone receptor gene in other species. The specification does not teach how to make knockout animals other than mice or correlate making knockout mice to other species. Therefore, the specification does not provide adequate guidance for one of skill in the art to make a transgenic, non-human animal or cells having a disruption in a nuclear hormone receptor gene in any species other than mice.

The specification does not provide adequate correlation between the phenotype obtained in mice to the phenotype obtained in other species. The state of the art at the time of filing was that the phenotype of transgenic mice does not predict the phenotype in non-mice species. Models of human diseases have relied on transgenic rats when the development of transgenic mice having the desired phenotype was not feasible. Mullins (1990, Nature, Vol. 344, pg 541-544) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse Ren-2 renin transgene. Hammer (1990, Cell, Vol. 63, pg 1099-1112) describes spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and

human b_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins, 1989, EMBO, Vol. 8, pg 4065-4072; Taurog, 1988, J. Immunol., Vol. 141, pg 4020-4023) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats. Therefore, the specification does not enable making transgenic having the disclosed phenotypes in species other than mice.

In addition, claims 17-29 do not provide a nexus between the disruption in nuclear hormone receptor and the phenotypes claimed. The claims do not recite the disruption of nuclear hormone receptor causes the phenotype claimed. The specification does not teach disrupting the nuclear hormone receptor gene in mice already lacking production of nuclear hormone receptor or in mice already having the phenotypes recited in claims 17-29. Given the art of transgenics at the time of filing taken with the guidance provided in the specification, the claim should reflect the fact that the phenotypes recited in claims 17-29 are a result of nuclear hormone receptor disruption. Otherwise, it would require one of skill undue experimentation to make the mouse as broadly claimed.

The specification does not enable making or using a transgenic with a wild-type phenotype as encompassed by claims 8, 11, 12 and 32-34. The transgenics in the claims do not recite any phenotype and may, therefore, have any phenotype including wild-type phenotype. The specification does not provide any use for a transgenic having a disruption in a nuclear hormone receptor gene that has a wild-type phenotype. The only disclosed phenotype for the transgenic

claimed is one that correlates to a disruption in a nuclear hormone receptor gene. Therefore, the claims should recite a non-wild-type phenotype that correlates to a disruption in a nuclear hormone receptor gene.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5-9, 11-15, 17-29, 31-35 and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of what applicants consider "nuclear hormone receptor" genes cannot be determined. The specification defines the term as any gene of SEQ ID NO:1 or having homology to SEQ ID NO:1 (pg 6, lines 24-29). However, not all genes sharing homology with SEQ ID NO:1 are nuclear hormone receptor genes.

Claims 17-29 and 38 are indefinite because they do not clearly set forth that the disruption in nuclear hormone receptor causes the phenotype.

Claims 21 and 26 are indefinite because it is unclear what "lymphoid depletion" is and whether it is a relative term that requires comparison to another type of mice, e.g. wild-type mice.

The metes and bounds of the "periarteriolar lymphoid sheaths" cannot be determined (claim 22).

The metes and bounds of "consistent with" are unclear. It is unclear if the mouse of claim 27 has "thymic dysplasia" or if the mouse has an abnormal

thymus. If claim 27 is limiting how the thymus is abnormal, the structure of the abnormal thymus cannot be determined. Claims 28 and 29 are included for the same reasons.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 5-9, 11-15, 17-29 and 31-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Kato (J. Biochem., May 2000, Vol. 127, pg 717-722).

Kato taught mice having a disruption in the nuclear hormone receptor gene VDR. The VDR gene is a nuclear hormone receptor gene as claimed because the specification defines a nuclear hormone receptor gene as sharing homology with SEQ ID NO:1 and because the VDR gene shares homology with SEQ ID NO:1. The mice were fed different diets, which are considered administering an agent as in claims 11-15 and 32-34, and tested for various organ abnormalities including spleen (pg 719, col. 1; pg 718, col. 2, 2nd ¶, last sentence).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5-9, 11-15 and 31-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi (Scientific American, 1994, Vol. 270, pg 34-41) in view of Choi (J. Biol. Chem., 1997, Vol. 272, pg 23565-23571).

Capecchi taught making a mouse having a disruption in a gene. Capecchi did not teach disrupting the nuclear hormone receptor gene.

However, Choi taught the nucleic acid sequence of the mouse nuclear hormone receptor gene of SEQ ID NO:1.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a transgenic mouse having a disruption in a gene as taught by Capecchi wherein the gene was the nuclear hormone receptor of SEQ ID NO:1 as taught by Choi. One of ordinary skill in the art at the time the invention was made would have been motivated to disrupt the nuclear hormone receptor gene instead of the gene disrupted by Capecchi to determine the function of the nuclear hormone receptor of SEQ ID NO:1 *in vivo*.

Thus, Applicants' claimed invention, as a whole is prima facie obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER